REMARKS

Entry of the foregoing amendments, in light of the following remarks, are respectfully requested.

Amendments

Claims 22 and 45 have been amended to limit the MMP inhibitor to those inhibiting MMP-1, as described below, and as supported at least by Fig. 5 and Figs. 7A-7F and the description of those figures in the specification.

Prior Art Rejection

The present claims stand rejected as obvious over Pikul in combination with Kumagai or Langholz, which rejection is respectfully traversed.

Submitted, and discussed in more detail below, are a declaration under 37 CFR § 1.132 by Dr. Fisher, a co-inventor, as well as copies of articles by Whittaker *et al.*, Vassiliou *et al.*, and Reiter *et al.*

Pikul is directed to a class of compounds, defined structurally, and *alleged* to inhibit MMPs. As discussed below and in Dr. Fisher's declaration, there is no evidence in Pikul that those compounds actually inhibit any MMP.

Pikul describes the "implication" that MPs are involved in tissue repair from "normal" injury such as scarring (col. 9, ln. 46-47, and col. 11, ln. 34-55). The only occurrence of the word "acne" is in claim 29 as "acne inflammation"; there is no other occurrence of "acne" in the specification. In short, Pikul provides no evidence that any of the suspect conditions are mediated by any specific MPs nor that the compounds disclosed therein actually inhibit any MP.

Kumagai describes certain flavone or anthocyanidin MMP inhibitors and does give some data on inhibition of collagenase (MMP-1) and a gelatinase B (MMP-9) *in vitro*. Acne is not disclosed in the reference.

Langholz is inapposite to the present invention. They describe contraction of collagen in a lattice model with amorphous collagen (as opposed to a structured environment in human skin). Human skin fibroblasts will naturally contract collagen until they are "comfortable" with the tension (and so can migrate through the collagen matrix). Some contraction is necessary in all skin healing, and the literature goes both ways as to whether MMPs are needed for contraction. Langholz states that genistein "reduced lattice contraction," which

would be contrary to the environment that fibroblasts want. There is no mention of acne in this reference.

While the cited art does describe genistein (and related compounds) as MMP inhibitors, there is no disclosure in any of the references that MMPs are elevated in acne lesions, nor *which* MMP(s) might be elevated in acne.

Regarding the utility of the Pikul compounds, Dr. Fisher (¶3.b.) states that he would have expected Pikul to provide *some* objective evidence that one of the Pikul compounds is actually an MMP inhibitor. As shown in the attached Whittaker article, mentioned in Dr. Fisher's declaration (¶3.c.), various compounds inhibit different MMPs to different degrees; some are selective for certain MMPs, and some may not inhibit certain other MMPs at all. Compound 66 in Whittaker (believed to be within the scope of the Pikul patent, and from the Pikul group) is more selective for MMP-13, MMP-8, and MMP-2 than for MMP-1. Further, the undersigned's quick review of the compounds in the Whittaker (109-118) shows that all other phosphinic acid inhibitors have a hydroxyl group attached to the phosphorous, unlike Pikul's compounds. The articles by Vassiliou and Reiter likewise have compounds with a hydroxyl attached to the phosphorous.

Table 1 in Whittaker (p. 2737) identifies some 20 different MMPs. Applicants claim a method of treatment. To have any reasonable basis for treating a conditioned believed to be mediated by MMPs, it is necessary to know which MMP(s) is active in the condition. None of the references shows any appreciation that in acne lesions MMP-1, as well as MMP-8, are elevated. Accordingly, the present claims have been limited to inhibiting MMP-1, which is a necessary and critical aspect based on the data in the present specification. Vassiliou is concerned with inhibiting MMP-11 (for treating invasive breast carcinoma), and Reiter is concerned with inhibiting MMP-13 (for treating osteoarthritis). The references are completely deficient in providing any motivation for inhibiting MMP-1 in acne lesions.

"Inflammation" exists in many medical conditions. Reiter is a good example because he is concerned with osteoarthritis, for which many "anti-inflammatories," especially those sold over-the-counter, are prescribed, advertised, and used. Yet Reiter (second paragraph) states that "MMP-13 is a

key driver of cartilage destruction (**vs MMP-1**)" (emphasis added). Again, knowledge of which MMP is active is a necessary prerequisite for treatment.

Thus, the mere use of genistein or quercetin, which Applicants acknowledge in the specification are known inhibitors of MMP-1, because such is confirmed by Kumagai and Langholz (or JP '628), does not provide any teaching or suggestion that such would be useful in treating acne scarring absent knowledge that (i) MMP-1 is elevated in acne lesions and (ii) the particular compound inhibits MMP-1.

Connective tissue of various types exists throughout the body. Given there are 20 known proteinases (MMPs) that degrade connective tissue does not render obvious the inhibition of a specific MMP for treating a specific condition. Accordingly, there is no reasonable expectation of success, as alleged in the rejection, unless one *first* has identified which (if any) MMP is elevated in a specific condition. Otherwise, given the Whittaker (and other art) disclosure of various selectivities of MMP inhibitors, determining which (if any) of those MMP inhibitors would be useful for treating a specific condition is only by trial and error. Such a hit or miss approach does not render obvious these claims.

The rejection based on the above references in combination with Segot provides no substantive additional teaching in this regard. Applicants have acknowledged that retinoids are well-known for treating acne (by both topical and systemic administration), and Segot is directed only to providing a stable retinol composition; there is no disclosure of the action of any MMP in acne. Thus, the additional use of a well-known active ingredient to an unobvious method using an inhibitor of a specific MMP would not have been obvious.

These amendments were not earlier presented because the Pikul reference with its minimal disclosure of "acne inflammation" was not previously of record. Nor do the present amendments raise any new issues as the prosecution thus far has clearly been directed to disclosures of MMP inhibitors and acne and inflammation.

In summary, none of the art renders obvious the selection of an inhibitor of MMP-1 for treating acne scarring. In light of the foregoing, withdrawal of the rejections are believed now to be in order, and such actions are earnestly solicited.